Complete Summary

GUIDELINE TITLE

Chemotherapeutic management of stage IV non-small cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Socinski MA, Morris DE, Masters GA, Lilenbaum R. Chemotherapeutic management of stage IV non-small cell lung cancer. Chest 2003 Jan;123(1 Suppl):226S-43S. [92 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Stage IV non-small cell lung cancer

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Oncology
Pulmonary Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To review the evidence supporting the role of systemic chemotherapy in the management of stage IV non-small cell lung cancer (NSCLC)

TARGET POPULATION

Patients with stage IV non-small cell lung carcinoma (NSCLC)

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment/Management

1. Referral to oncology specialist
2. Assessment of performance status using standard scales (e.g., European Cooperative Oncology Group [ECOG] scale) to select suitable candidates for chemotherapy
3. First-line therapy using cisplatin- or carboplatin-based agent and one of the new agents (paclitaxel, vinorelbine, gemcitabine, docetaxel)
4. Second-line chemotherapy for patients with good performance status and disease progression after receiving platinum-based therapy
5. Best supportive care
6. Consideration of patient´s preferences and attitudes in choosing chemotherapy

MAJOR OUTCOMES CONSIDERED

- Response rate
- Survival (median, 1-year, and progression-free)
- Palliation of symptoms
- Quality of life
- Toxicity of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Overview

As a first step in identifying the evidence for each topic, the guideline developers sought existing evidence syntheses including guidelines, systematic reviews, and meta-analyses. They searched computerized bibliographic databases including MEDLINE, Cancerlit, CINAHL and HealthStar, the Cochrane Collaboration Database of Abstracts of Reviews of Effectiveness, the National Guideline Clearinghouse, and the National Cancer Institute Physician Data Query database. Computerized searches through July 2001 used the MeSH terms lung neoplasms (exploded) and bronchial neoplasms or text searches for lung cancer combined with review

articles, practice guidelines, guidelines, and meta-analyses. They also searched and included studies from the reference lists of review articles, and queried experts in the field. An international search was conducted of Web sites of provider organizations that were likely to have developed guidelines. Abstracts of candidate English language articles were reviewed by two physicians (one with methodological expertise and one with content area expertise) and a subset was selected for review in full text. Full-text articles were reviewed again by two physicians to determine whether they were original publications of a synthesis and were pertinent to at least one of the topics of the guideline. Articles described as practice guidelines, systematic reviews, or meta-analyses were included, as were review articles that included a "Methods" section. Included articles were classified according to topic.

Strategy Specific for Chemotherapeutic Management of Stage IV Non-small Cell Lung Cancer

For the topic on chemotherapeutic management of stage IV non-small cell lung cancer, the guideline developers formulated eleven key questions that were to be answered by a comprehensive critical review of the published evidence (see Guideline) using the following search terms: age and lung cancer; antineoplastic agents, combined; carcinoma, non-small cell lung; carcinoma, non-small cell lung/drug therapy; carcinoma, non-small cell lung/therapy; chemotherapy; clinical trials; combination chemotherapy; duration of therapy; lung neoplasms; lung neoplasms/drug therapy; lung neoplasms/therapy; outcomes; performance status and lung cancer; prognosis factors and lung cancer; prognosis and lung cancer; prognosis and non-small cell lung cancer; quality of life and lung cancer; randomized trials; sex and lung cancer; stage IV non-small cell lung cancer; weight loss and lung cancer. In addition, the primary evidence was supplemented by the authors if data sources were identified outside the MEDLINE search mechanism.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The United States Preventive Services Task Force (USPSTF) scheme offers general guidelines to assign one of the following grades of evidence: good, fair, or poor. In general, good evidence included prospective, controlled, randomized clinical trials, and poor evidence included case series and clinical experience. Trials with fair quality of evidence, for instance, historically controlled trials or retrospective analyses, were somewhere in between. In addition to the strength of the study design, however, study quality also was considered. The United States Preventive Services Task Force approach considers well-recognized criteria in rating the quality of individual studies for a variety of different types of study design (e.g.,

diagnostic accuracy studies and case-control studies). The thresholds for distinguishing good vs fair and fair vs poor evidence are not explicit but are left to the judgment of panelists, reviewers, and members of the executive committee.

Assessment of the Scope and Quality of Clinical Practice Guidelines

Clinical practice guidelines identified from the systematic search were evaluated by at least four reviewers using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Informal Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Each writing committee received a comprehensive list of existing systematic reviews and meta-analyses as well as guidelines published by other groups. In addition, for five key topics (prevention, screening, diagnosis, and staging [invasive and noninvasive]), new systematic reviews were undertaken (see "Description of Methods Used to Collect the Evidence" and "Description of Methods Used to Analyze the Evidence" fields). For all other topics, writing committees were responsible for identifying and interpreting studies that were not otherwise covered in existing syntheses or guidelines.

The guidelines developed by the writing committee were distributed to the entire expert panel, and comments were solicited in advance of a meeting. During the meeting, proposed recommendations were reviewed, discussed, and voted on by the entire panel. Approval required consensus, which was defined as an overwhelming majority approval. Differences of opinion were accommodated by revising the proposed recommendation, the rationale, or the grade until consensus could be reached. The evidence supporting each recommendation was summarized, and recommendations were graded as described. The assessments of level of evidence, net benefit, and grade of recommendation were reviewed by the executive committee.

Values

The panel considered data on functional status, quality and length of life, tolerability of treatment, and relief of symptoms in formulating guideline recommendations. Cost was not explicitly considered in the guideline development

process. Data on these outcomes were informally weighted, without the use of explicit decision analysis or other modeling. The values placed on types of outcomes varied with clinical scenarios. For example, in some situations they considered life expectancy, such as the effects of early detection. In other situations they weighed quality of life more heavily, such as in palliative care and in interpreting small increases in life expectancy with chemotherapy for stage IV disease.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The guideline developer´s grading scheme is a modification of the United States Preventive Services Task Force (USPSTF) grades to allow recommendations for a service when (1) evidence is poor, (2) the assessment of the net benefit is moderate to high, and (3) there is consensus among the expert panel to recommend it. This change was necessary because, unlike preventive services (i.e., the routine offering of tests or treatments to well people) in which the burden of proof is high, clinical decisions about the treatment of patients with lung cancer often must be based on an interpretation of the available evidence, even if it is of poor quality. This adaptation distinguished between interventions with poor evidence for which there is consensus (grade C) and interventions with poor evidence for which there is not consensus (grade I).

Grades of Recommendations and Estimates of Net Benefit

The grade of the strength of recommendations is based on both the quality of the evidence and the net benefit of the service (i.e., test, procedure, etc).

Grade A The panel strongly recommends that clinicians routinely provide [the service] to eligible patients. An "A" recommendation indicates good evidence that [the service] improves important health outcomes and that benefits substantially outweigh harms.

Grade B The panel recommends that clinicians routinely provide [the service] to eligible patients. A "B" recommendation indicates at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.

Grade C The panel recommends that clinicians routinely provide [the service] to eligible patients. A "C" recommendation indicates that there was consensus among the panel to recommend [the service] but that the evidence that [the service] is effective is lacking, of poor quality, or conflicting, or the balance of benefits and harms cannot be reliably determined from available evidence.

Grade D The panel recommends against clinicians routinely providing [the service]. A "D" recommendation indicates at least fair evidence that [the service] is ineffective or that harm outweighs benefit.

Grade I The panel concludes that the evidence is insufficient to recommend for or against [the service]. An "I" recommendation indicates that evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of

benefits and harms cannot be determined, and that the panel lacked a consensus to recommend it.

Net Benefit

The levels of net benefit are based on clinical assessment. Estimated net benefit may be downgraded based on uncertainty in estimates of benefits and harms.

Substantial Benefit: Benefit greatly outweighs harm

Moderate Benefit: Benefit outweighs harm

Small/weak Benefit: Benefit outweighs harm to a minimally clinically important degree

None/negative Benefit: Harms equal or outweigh benefit, less than clinically important

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After extensive review within the expert panel and executive committee, the guidelines were reviewed and approved by the American College of Chest Physicians (ACCP) Health and Science Policy Committee and then by the American College of Chest Physicians Board of Regents.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation is rated based on the levels of evidence (good, fair, poor), net benefit (substantial, moderate, small/weak, none/negative), and the grades of the recommendations (A, B, C, D, I). Definitions are presented at the end of the "Major Recommendations" field.

1. When selecting patients for systemic chemotherapy, performance status (PS) at the time of diagnosis should be used because it is a consistent prognostic factor for survival. Patients with a PS of Eastern Cooperative Oncology Group (ECOG) 0 or 1 should be offered chemotherapy. Level of evidence, good; benefit, substantial; grade of recommendation, A. Data are not yet sufficient to routinely recommend chemotherapy to patients with a PS of ECOG level 2 Level of evidence, poor; benefit, small/weak; grade of

recommendation, I. Patients with a PS of ECOG level 3 or 4 should not receive chemotherapy (level of evidence, fair; benefit, moderate; grade of recommendation, B). Other patient-related factors (e.g., gender, age, sites of metastases, or histology) have not been consistent prognostic factors for survival. Level of evidence, poor; benefit, small/weak; grade of recommendation, I

2. Patients with good PS (i.e., ECOG level 0 or 1) should be considered for a platinum-based chemotherapy regimen based on the survival advantage provided over best supportive care (BSC). Level of evidence, good; benefit, substantial; grade of recommendation, A
3. Although new agents demonstrate improved survival compared to best supportive care (level of evidence, good; benefit, moderate; grade of recommendation, B) in elderly patients as well as in nonelderly patients with advanced non-small cell lung cancer (NSCLC), the data are not yet sufficient to compare the new single agents to platinum-based combination therapies. Level of evidence, poor; benefit, small/weak; grade of recommendation, I
4. Combination chemotherapy regimens incorporating the new single agents with a platinum agent should be considered the standard of care. Level of evidence, fair; benefit, moderate; grade of recommendation, B
5. No one regimen has been demonstrated to be superior in the first-line therapy for patients with advanced NSCLC. A cisplatin-based or carboplatin-based combination regimen that includes one of the new agents remains the standard of care for first-line therapy in patients with stage IV NSCLC. Level of evidence, good; benefit, substantial; grade of recommendation, A
6. The duration of first-line therapy in patients with stage IV NSCLC should be brief, consisting of 3 to 4 cycles or fewer if there are signs of progressive disease. Level of evidence, good; benefit, substantial; grade of recommendation, A
7. Patients with a good PS in whom disease progresses after receiving platinum-based chemotherapy should be offered second-line chemotherapy. Level of evidence, good; benefit, moderate; grade of recommendation, B
8. Data from case series and randomized trials show that chemotherapy can have a palliative effect on disease-related symptoms and can improve quality of life (QOL) compared to best supportive care in stage IV NSCLC patients who are deemed suitable for treatment. Level of evidence, good; benefit, moderate; grade of recommendation, B
9. Patient preferences need to be considered and respected with regard to the decision to treat with chemotherapy. Most patients would not choose chemotherapy for a likely survival of 3 months or a <10% improvement in the 1-year survival rate unless there was an improvement in quality of life. No patient variables have been identified to determine an individual patient´s minimum threshold to accept chemotherapy, and therefore the decision to treat with chemotherapy needs to be discussed with each patient individually. Level of evidence, fair; benefit, moderate; grade of recommendation, B
10. Patients with stage IV NSCLC should be referred to a physician with specialized training in oncology. If chemotherapy is considered to be appropriate, adequate resources to administer chemotherapy safely must be available. Level of evidence, poor; benefit, substantial; grade of recommendation, C
11. Combination platinum-based chemotherapy can be administered safely and with acceptable and manageable toxicity profiles in patients with good PS who

have stage IV NSCLC. Level of evidence, good; benefit, substantial; grade of recommendation, A

Definitions:

Levels of Evidence

In general, good evidence included prospective, controlled, randomized clinical trials, and poor evidence included case series and clinical experience. Trials with fair quality of evidence, for instance, historically controlled trials or retrospective analyses, were somewhere in between.

Grades of Recommendations and Estimates of Net Benefit

The grade of the strength of recommendations is based on both the quality of the evidence and the net benefit of the service (i.e., test, procedure, etc).

Grade A The panel strongly recommends that clinicians routinely provide [the service] to eligible patients. An "A" recommendation indicates good evidence that [the service] improves important health outcomes and that benefits substantially outweigh harms.

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Grade C The panel recommends that clinicians routinely provide [the service] to eligible patients. A "C" recommendation indicates that there was consensus among the panel to recommend [the service] but that the evidence that [the service] is effective is lacking, of poor quality, or conflicting, or the balance of benefits and harms cannot be reliably determined from available evidence.

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None/negative Benefit: Harms equal or outweigh benefit, less than clinically important

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Evidence has shown that chemotherapy improves survival and palliates symptoms, thereby improving quality of life (QOL) in patients in both the first-line and second-line treatment setting. In addition, selecting patients based on their performance status (PS) helps to identify patients significantly compromised by their disease and who may not benefit from therapy and/or may experience excessive toxicity.

POTENTIAL HARMS

Chemotherapy can produce toxic effects. The major toxicities are hematologic, with neutropenia being the predominant adverse effect. Despite this, the clinical consequences of severe neutropenia (i.e., sepsis) occur in < 10% of patients, and the treatment-related death rates in these studies ranged from 0 to 4%. Severe anemia occurs in 7 to 30% of patients. Severe thrombocytopenia varies depending on the regimen used as well as on the dose and schedule of the agents in the regimen. However, bleeding complications are unusual. Nonhematologic toxicity consists mainly of nausea/vomiting, fatigue, and alopecia. In the more recent trials employing modern antiemetic regimens or using carboplatin rather than cisplatin, the rates of severe nausea/vomiting range from 7 to 20%. The toxicity profiles of single agents are somewhat less than those of combination regimens and can be found in the individual references provided in the original guideline document. It should also be noted that the risk of toxicity increases in patients with performance status (PS) 2.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

1. The American College of Chest Physicians (ACCP) is developing a set of PowerPoint slide presentations for physicians to download and use for physician and allied health practitioners education programs.
2. The ACCP is developing a Quick Reference Guide (QRG) in print and PDA formats for easy reference.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Socinski MA, Morris DE, Masters GA, Lilenbaum R. Chemotherapeutic management of stage IV non-small cell lung cancer. Chest 2003 Jan;123(1 Suppl):226S-43S. [92 references]

ADAPTATION

Not applicable: Guideline was not adapted from another source.

DATE RELEASED

2003 Jan

GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

GUIDELINE DEVELOPER COMMENT

The guideline development panel was composed of members and nonmembers of the American College of Chest Physicians (ACCP) who were known to have expertise in various areas of lung cancer management and care, representing multiple specialties from the following 13 national and international medical associations:

- Alliance for Lung Cancer Advocacy, Support, and Education (a patient support group)

- American Association for Bronchology
- American Cancer Society
- American College of Physicians
- American College of Surgeons Oncology Group
- American Society of Clinical Oncology
- American Society for Therapeutic Radiology and Oncology
- American Thoracic Society
- Association of Community Cancer Centers
- Canadian Thoracic Society
- National Comprehensive Cancer Network
- Oncology Nurses Society
- Society of Thoracic Surgeons

The specialties included pulmonary/respiratory medicine, critical care, medical oncology, thoracic surgery, radiation oncology, epidemiology, law, and medical ethics.

SOURCE(S) OF FUNDING

Funding for both the evidence reviews and guideline development was provided through an unrestricted educational grant from Bristol-Myers Squibb, which had no other role in the evidence review or guideline development process or content.

GUIDELINE COMMITTEE

American College of Chest Physicians (ACCP) Expert Panel on Lung Cancer Guidelines

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Mark A. Socinski, MD, FCCP; David E. Morris, MD; Gregory A. Masters, MD, FCCP; Rogerio Lilenbaum, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Information about potential conflicts of interest were collected from each member of the expert panel or writing committee at the time of their nomination in accordance with the policy of the American College of Chest Physicians. Information on conflicts of interest for each panelist is listed in the guideline.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available to subscribers of Chest - The Cardiopulmonary and Critical Care Journal.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

Background Articles

- Alberts WM. Lung cancer guidelines. Introduction. Chest 2003 Jan;123(1 Suppl):1S-2S
- McCrory DC, Colice GL, Lewis SZ, Alberts WM, Parker S. Overview of methodology for lung cancer evidence review and guideline development. Chest 2003 Jan;123(1 Suppl):3S-6S.
- Harpole LH, Kelley MJ, Schreiber G, Toloza EM, Kolimaga J, McCrory DC. Assessment of the scope and quality of clinical practice guidelines in lung cancer. Chest 2003 Jan;123(1 Suppl):7S-20S.
- Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest 2003 Jan;123(1 Suppl):21S-49S.

Electronic copies: Available to subscribers of Chest - The Cardiopulmonary and Critical Care Journal.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 3, 2003. The information was verified by the guideline developer on October 1, 2003.

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